NMP

N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.

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December 20, 2019

Via E-Mail

Mr. Mark A. Hartman
Deputy Director for Management
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 7403M)
Washington, DC 20460

Re: EPA Request for Submission of NMP Study Reports -- Following Up on December 11, 2019, EPA Response to NMP Producers Group

Dear Mr. Hartman:

The N-Methylpyrrolidone (NMP) Producers Group submits this letter and the appended documents in response to your December 11, 2019, letter. The NMP Producers Group appreciates your and other U.S. Environmental Protection Agency (EPA) staff's efforts in addressing our concerns related to members' desire to protect their proprietary interests in the studies being requested by EPA. Unfortunately, your letter offered no workable solutions to the NMP Producers Group situation. We note again that the NMP Producers Group situation is not unique and that many other industry groups engaged in Toxic Substances Control Act (TSCA) actions have similar concerns on study report protection. We urge EPA to work with us and others to find a viable solution that will reasonably meet stakeholders' needs.

According to your letter, if the NMP Producers Group provides the full reports for the studies in question, EPA is unable to ensure that the reports will not be publicly disclosed. You state that this inability to protect the reports is due to EPA's interpretation of TSCA Section 14 and requirements under the Freedom of Information Act (FOIA). The NMP Producers Group has not conducted a legal analysis of EPA's positions and will not be commenting on them in this letter. We may, however, choose to challenge these positions in the future.

Your letter also invited NMP Producers Group members to consider including an assertion of ownership rights with any report submitted to EPA to avoid further use by third parties without authorization. You further state that "(o)ther study owners have taken such an approach and found success in similar circumstances…." While we appreciate EPA's suggestion, we question on what exactly EPA bases its claim of "success" by other study owners. Has EPA conducted a comprehensive analysis of whether these reports were submitted to other regulatory jurisdictions, and if so, what those government agencies' responses were? Does EPA

know what parties have downloaded the reports in question, and has EPA followed up with those parties on how the reports will be used? We anticipate the answers to these questions is "no," and we are aware of no independent, empirical evidence to support EPA's optimism.

EPA must under TSCA use the *best available science* in its NMP risk evaluation. To comply, EPA must consider the data generated in the two reproductive toxicity studies sponsored by the NMP Producers Group (NMP Producers Group, 1999a and 1999b). This point was reinforced by members of the Science Advisory Committee on Chemicals (SACC) during its review meeting on December 5 and 6, 2019. Your December 11, 2019, letter states that EPA is already in possession of a "high-quality" study on reproductive toxicity and implies that the NMP Producers Group data are not necessary. Although not specifically stated in your letter, we assume the "high-quality study" that you are referring to is the Exxon 1991 study on which EPA has proposed relying for identifying the critical end point in the draft NMP risk evaluation. We note that the Exxon study cannot be considered a "high-quality" study for the following reasons:

- The mating schedule in the Exxon 1991 study was problematic because the animals had differing numbers of opportunities to mate. This method of breeding does not encounter problems as long as there is not a higher than normal incidence of infertile male or female rats within the test population. This was not the case with the Exxon 1991 study. The revised EPA Test Guidelines recognize that fertility is a "couples-specific" phenomenon and can only be evaluated based on single mating pairs, rather than multiple opportunities to mate with several partners.

- Complicating the mating schematic used in the Exxon study was the increased probability of brother:sister matings, given that both the male and female rats used in this study came from the same room within the same breeding facility.

- Additionally, the specific Charles River site where the rats from the Exxon study originated had fertility problems at the same time (fall of 1989) that the study was ongoing.

- By the end of the first (P1) generation, the number of females available for mating at each dose level group had dropped from 30 at the start of the study to between 13 and 16 at the start of the P2 generation. Even in the control group, there was a 47% reduction in females available for mating over the course of one generation. This suggests that there was something seriously wrong with this population of test animals.

- To generate the protocol-required group size of 30 males and 30 females, the study director needed to select more than 2 males and 2 females from certain litters from the 500 mg/kg/day group.[1] While this is a relatively minor point, it illustrates several points of concern. First, it becomes much more difficult to avoid brother:sister matings in the P2 generation within the 500 mg/kg/day group. Second, due to the smaller number of animals available for breeding, the overall population of animals in the P2 generation is becoming more inbred and therefore more likely to experience reproductive failure.

- In addition, during the course of the study, laboratory personnel did not detect the mating of some animals. The authors of the Exxon study did not include pregnant females for which mating confirmation had been missed by personnel within the fertility and fecundity indices. This indicates that some animals were fertile (as they were pregnant or the females they were paired with were pregnant) but were not included within the calculations simply due to the fact that the laboratory personnel did not detect the mating of the animals. The lack of inclusion of non-confirmed mated females who were pregnant and the use of multiple matings to different animals suggests that the calculations used to prepare the mating and fertility indices for this study are questionable.

- EPA, as the sponsoring authority for NMP at the Organization of Economic Development and Cooperation (OECD) SIDS Initial Assessment Meeting knows that the international regulatory authorities rated the Exxon study (reliability score of 2) inferior in quality to those conducted by the NMP Producers Group (reliability scores of 1).

- Most importantly, EPA's position that the fertility/fecundity effects in the Exxon study are "biologically significant" is not supported by the two additional two-generation reproductive toxicity studies sponsored by the NMP Producers Group, which had the higher quality ranking score, nor is it supported by the other studies cited by EPA as providing such support (Sitarek *et al.* 2012 and Sitarek and Stetkiewicz 2008).

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[1] In the 500 mg/kg/day group, there were only 13 litters, and therefore only 26 male and 26 female rats in this group were available for selection to populate the P2 (F1b) parents, even though the protocol called for 30 each.

The NMP Producers Group voluntarily conducted the two additional reproductive toxicity studies to improve the available information on NMP, and we want EPA to use the information generated in its risk evaluation. It was always the Group's intent that the data would be considered for applicable regulatory purposes. We continue, however, to request that the study reports be protected. Members should not be forced to choose between the consequences of EPA's failure to comply with the law and sacrificing the Group's legitimate rights to confidentiality.

As we have noted in prior communications with EPA, the findings of these study reports are not claimed as confidential. Indeed, the reports in question have robust summaries of the testing program, and the key data points and scientific conclusions are prepared and publicly posted. It is not the information in the study report that needs to be protected from public dissemination. It is the study report itself that has the monetary value, as it is required for registration purposes in other government jurisdictions but is not publicly posted.

While we do not agree with EPA's position on public sharing of the study report, we do believe that there is another option. The NMP Producers Group is willing to share the relevant raw data from the study for EPA assessment purposes. These data, coupled with the robust study summary, should be sufficient for EPA and other knowledgeable stakeholders to judge the quality of the studies and the conclusions reached. The relevant information will be available to those with expertise to make meaningful and informed judgments on the study results.

To progress this important dialogue, the NMP Producers Group is proactively providing you with the robust study summary and raw data for the following study of interest to EPA:

- NMP Producers Group (1999a). Two-generation reproduction toxicity study with N-Methylpyrrolidone (NMP) in Sprague-Dawley rats -- Administration in the diet. Huntingdon Life Sciences, East Millstone, NJ, Project No.: 97-4106, unpublished report.

  The raw data pulled from the report in question includes

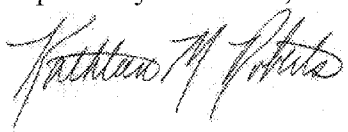
  - Individual male and female findings,
  - Organ weights,
  - Corpora lutea and ovarian follicular counts,
  - Pup observations, and

- Tables for
  - Mating indices, pregnancy rates, and male fertility indices;
  - Gestation length, parturition data, and litter data;
  - Pup body weight -- data during lactation;
  - Pup and litter survival indices; and
  - Pup sex distribution data.

If EPA finds this submission acceptable for TSCA purposes, the NMP Producers Group would be pleased to provide the summary and data from the other study in question.

The NMP Producers Group would appreciate EPA's prompt consideration of this approach as it has implications on how the Group will proceed related to its comments on the draft risk evaluation. If needed, we would be pleased to meet with you to discuss this approach further.

Respectfully submitted,



Kathleen M. Roberts
NMP Producers Group Manager

cc: David B. Fischer, Esquire (EPA)
Stanley Barone, Jr., Ph.D. (EPA)
Ana Corado (EPA)

Attachments

Reference List

Exxon Biomedical Sciences. 1991. Multigeneration rat reproduction study with N-methylpyrrolidone. Project No. 236535, Nov. 26. Wayne, NJ: GAF Corp.

NMP Producers Group. 1999a. Two generation reproduction toxicity study with N-methylpyrrolidone (NMP) in Sprague Dawley rats: Administration in the diet. (Project No. 97-4106). Millstone, NJ: Huntingdon Life Sciences.

NMP Producers Group. 1999b. Two Generation Reproduction Toxicity Study with N-Methylpyrrolidone (NMP) in Wistar Rats - Administration in the Diet. (Project No. 70R0056/97008). Ludwigshafen, Germany: Department of Toxicology of BASF Aktiengesellschaft.

OECD. 2007. SIDS initial assessment report on 1-methyl-2-pyrrolidone. Washington, DC: Organization for Economic Cooperation and Development.

Sitarek, K., Stetkiewicz, J. 2008. Assessment of reproductive toxicity and gonadotoxic potential of N-methyl-2-pyrrolidone in male rats. Int. J. Occup. Med. Environ. Health 21(1): 73-80. doi: 10.2478/v10001-008-0006-z.

Sitarek, K., Stetkiewicz, J., Wąsowicz, W. 2012. Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone. Birth Defects Res. B Dev. Reprod. Toxicol. 95(3): 195-201. doi: 10.1002/bdrb.21001.